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Repeated Radiofrequency Ablation Combined With Ablated Lesion Elimination and Transarterial Chemoembolization Improves the Outcome of Solitary Huge Hepatocellular Carcinomas 10 cm or Larger

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Abstract: This study investigated the effectiveness of a new strategy, repeated radiofrequency (RF) ablation combined with ablated lesion elimination following transarterial chemoembolization (TACE)/transarterial embolization (TAE), for solitary huge hepatocellular carcinoma (SHHCC) 10 cm or larger.

From July 2008 to October 2015, 39 consecutive patients with SHHCC were screened. Of these, 12 were treated with TACE/TAE and repeated RF ablation (TACE/TAE + RF ablation group) and the remaining 27 patients were treated with the aforementioned new strategy (new strategy group). Local tumor progression (LTP)-free survival, intrahepatic distant recurrence (IDR)-free survival, and overall survival (OS) rates were obtained using the Kaplan–Meier method. Univariate and multivariate analyses were performed on several clinicopathological variables to identify factors affecting long-term outcome and intrahepatic recurrence. Correlation analysis was also performed.

The 1-, 2-, and 3-year LTP-free survival rates and OS rates were significantly higher in the new strategy group than in the TACE/TAE + RF ablation group (82.9% vs 58.3%, 73.9% vs 29.2%, 18.5% vs 9.7%, $P=0.002$; 92.0% vs 75.0%, 84.0% vs 33.3%, 32.7% vs 16.7%, $P=0.025$). However, there was no significant difference between the 2 groups in the 1-, 2-, and 3-year IDR-free survival rates ($P=0.108$).

Using univariate analysis, alpha-fetoprotein (AFP > 200 ng/mL), ablative margin (AM > 1.0 cm), and well-differentiated cells were found to be significant factors for predicting LTP, IDR, and OS. Surgical elimination was found to be a significant factor only for predicting OS. In multivariate analyses, AFP (>200 ng/mL), AM (>1.0 cm), and well-differentiated cells were found to be significant independent factors linked to LTP, IDR, and OS. Correlation analysis indicated that AM > 1.0 cm was strongly associated with surgical elimination ($P<0.001$, correlation coefficient = 0.877).

For patients with SHHCC who were initially excluded from surgery, the new strategy including repeated RF ablation combined with ablated lesion elimination following TACE/TAE should now be considered as an alternative treatment.

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Abbreviations: AM = ablative margin, HCC = hepatocellular carcinoma, IDR = intrahepatic distant recurrence, LTP = local tumor progression, OS = overall survival, RF = radiofrequency, SHHCC = solitary huge hepatocellular carcinoma, TACE = transarterial chemoembolization, TAE = transarterial embolization.

INTRODUCTION

Hepatocellular carcinoma (HCC) accounts for more than 90% of primary liver cancer and ranks the 3rd most common cause of cancer-related death in the world.^{1,2} There is a drastically high prevalence of HCC in south eastern Asia and Africa and increasing prevalence in Western countries, with an annual incidence of more than 1 million worldwide.^{1,3,4}

There are remarkable evolutions in the development of therapeutic modalities for treating HCC over the past decade. HCC diagnosed at an early stage has a relatively good prognosis.^{1,5} Unfortunately, a majority of patients with HCCs are diagnosed at very advanced stage of disease with a tumor size more than 5 cm due to patients' ignorance of the importance of routine HCC screening. Many patients even present at the clinic with a symptomatic HCC mass larger than 10 cm.^{6,7} Large HCCs at very advanced stage are usually complicated with intra- or extrahepatic metastases or gross venous invasion.⁸ However, among huge HCCs, some subtypes of tumors present as solitary mass growing expansively within an intact capsule or pseudocapsule, without major venous invasion.^{9,10} Such subtypes of solitary huge HCCs (SHHCCs) still have the chance to be eradicated with the goal of achieving a prolonged survival.

Currently, how to select an optimal treatment for SHHCC remains in debate. It was reported that hepatic resection could be performed safely for well-selected SHHCC patients with low

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mortality and favorable survival outcomes.^{8,10–12} However, only extremely small number of patients with SHHCC could receive the treatment of surgical resection. It is a challenging task to safely resect the tumor mass to achieve a positive outcome for patients with SHHCC. In addition, patients with SHHCC are excluded the chance of liver transplantation. Palliative treatments, such as transarterial chemoembolization (TACE) or transarterial embolization (TAE) or systemic administration of sorafenib, provide marginal survival benefit.^{13,14}

Radiofrequency (RF) ablation has been established as 1 of the most promising locoregional therapies for treating early stage HCC.^{1,15,16} Traditionally, RF ablation is performed as an alternative treatment of surgical resection for managing HCC smaller than 5 cm in the largest diameter. Repeated RF ablations of huge HCCs have been increasingly carried out in many centers with the attempt of expanding the usage of RF ablation to treat HCC.^{17–19} In recent years, we have tried to use a combination therapy of RF ablation with TACE to treat SHHCC. Our primary results indicated that repeated RF ablation can be recommended for patients with SHHCC who are not suitable for surgery or refuse to receive surgical tumor removal, with acceptable efficacy and safety.⁹ However, tumor recurrence or local tumor progression (LTP) remains a critical clinical issue for those patients with SHHCC who even achieved imaging-confirmed complete ablation. The most possible reason for high incidence of tumor recurrence lies in the fact that it is very difficult to obtain a sufficient ablative margin (AM) for such huge HCCs using repeated ablation alone. Between July 2008 and October 2015, we treated patients with SHHCC with a new strategy of RF ablation combined with TACE. The efficacy of reducing the rate of tumor recurrence or LTP and safety of this treatment were retrospectively evaluated.

MATERIALS AND METHODS

Patients

Patients involved in this study were treated in the following hospitals in China: Beijing Chaoyang Hospital Affiliated to Capital Medical University, Beijing, China; Fenyang Hospital, Shanxi, China; Zhanhua People's Hospital, Shandong, China; Chaoyang Central Hospital, Liaoning, China; Chifeng University Affiliated Hospital, Neimenggu, China; and Shanxi Provincial People's Hospital, Shanxi, China. The ethics committee in each institution approved the study in compliance with the standards of the Declaration of Helsinki and the current practice and guidelines in China. In addition, all research personnel and collaborators who participated in this study were well trained accordingly.

From July 2008 to October 2015, 2415 patients were diagnosed with HCC at the outpatient clinics of the 6 institutions. Among them, 132 patients were diagnosed with SHHCC. The diagnostic criteria were as follows: solitary tumor mass with a size ≥ 10 cm growing expansibly within an intact capsule or pseudocapsule; absence of portal vein thrombosis; and no obvious satellite lesion or extrahepatic metastasis appearing on pretreatment images. Seventy-five patients who did not have contraindications of surgical resection were treated by hepatic resection. Eighteen patients who have no chance of surgery were treated with TACE/TAE, sorafenib, or supportive care. Thirty-nine patients received RF ablation-based treatments with the following criteria: unresectable lesion or patient's refusal of receiving surgical resection; no prohibitive comorbidities; and patients with a favorable Child–Pugh grade (grade A plus selected grade B). Written informed consent was obtained from

patients before treatment. Between July 2008 and October 2011, patients with SHHCC were treated by TACE/TAE followed by repeated RF ablation (TACE/TAE + RF ablation group). From November 2011 to October 2015, a new strategy was developed, in which repeated RF ablation combined with simultaneous surgical elimination of the ablated lesion and involution of the residual tumor, followed by TACE/TAE (Figures 1 and 2) (new strategy group). All procedures were performed by the same experienced operator (W-BS).

In the TACE/TAE + RF ablation group, diagnosis of HCC was histologically confirmed by fine needle aspiration biopsy under computed tomography (CT) guidance. In the new strategy group, HCC diagnosis was confirmed by histopathological examination of surgical samples. The pretreatment assessments of each patient include medical history, physical examination, laboratory test of whole blood count, prothrombin time and serum alpha-fetoprotein (AFP), biochemistry tests for renal and liver function evaluation, electrocardiogram, and chest X-ray. Abdominal ultrasound and spiral CT or magnetic resonance imaging (MRI) of the abdomen were performed for evaluation of the tumor status.

TACE/TAE

TACE/TAE was used to either downsize the tumor or decrease the tumor vascularity 3 to 4 weeks before RF ablation (TACE for Child–Pugh grade A; TACE or TAE for grade B). TACE/TAE was performed as we described previously.⁹

Ablation Strategies

We performed different treatment strategies of RF ablation for patients in the 2 groups. In the TACE/TAE + RF ablation group, we used the procedures described previously.⁹ Briefly, a primary central massive ablation was performed, followed by peripheral repeated RF ablations. In the new strategy group, a treatment strategy including sequential treatments was carried out in 3 phases.

Phase 1: Primary Tumor Ablation

Percutaneous RF ablation was the preferable therapy for SHHCC in this phase. RF ablation was repeated 2 to 4 times as needed based on the tumor status evaluated by abdominal contrast-enhanced CT or MRI. CT-guided RF ablation was performed using Cool-tip ACTC1525 or ACTC2025 electrodes under general anesthesia as described previously.⁹ An RF generator (Covidien Healthcare, Dublin, Republic of Ireland) was used for RF ablation according to the manufacturer's protocol. We selected the appropriate electrode based on the size, geometry, and location of the index tumor. With a 2.5-cm exposed tip, a Cool-tip electrode can produce an ablation zone of 4.5 cm in diameter with a single placement and maximum power of 200 W. The ablation was applied to the tumor for 15 to 20 min, which was slightly longer than the treatment duration recommended by the manufacturer's protocol, with the purpose of achieving the maximal ablated tumor zone. For multiple sessions of RF ablations, overlapped ablations were performed to warrant the substantial tumor ablation. The electrode track was ablated to minimize the likelihood of postablation bleeding and tumor seeding.

Phase 2: Surgical Elimination of the Ablated Lesion and Involution of the Remnant Tumor

To guarantee a sufficient AM, we deliberately eliminated the ablated lesion and decreased the volume of remnant tumor as

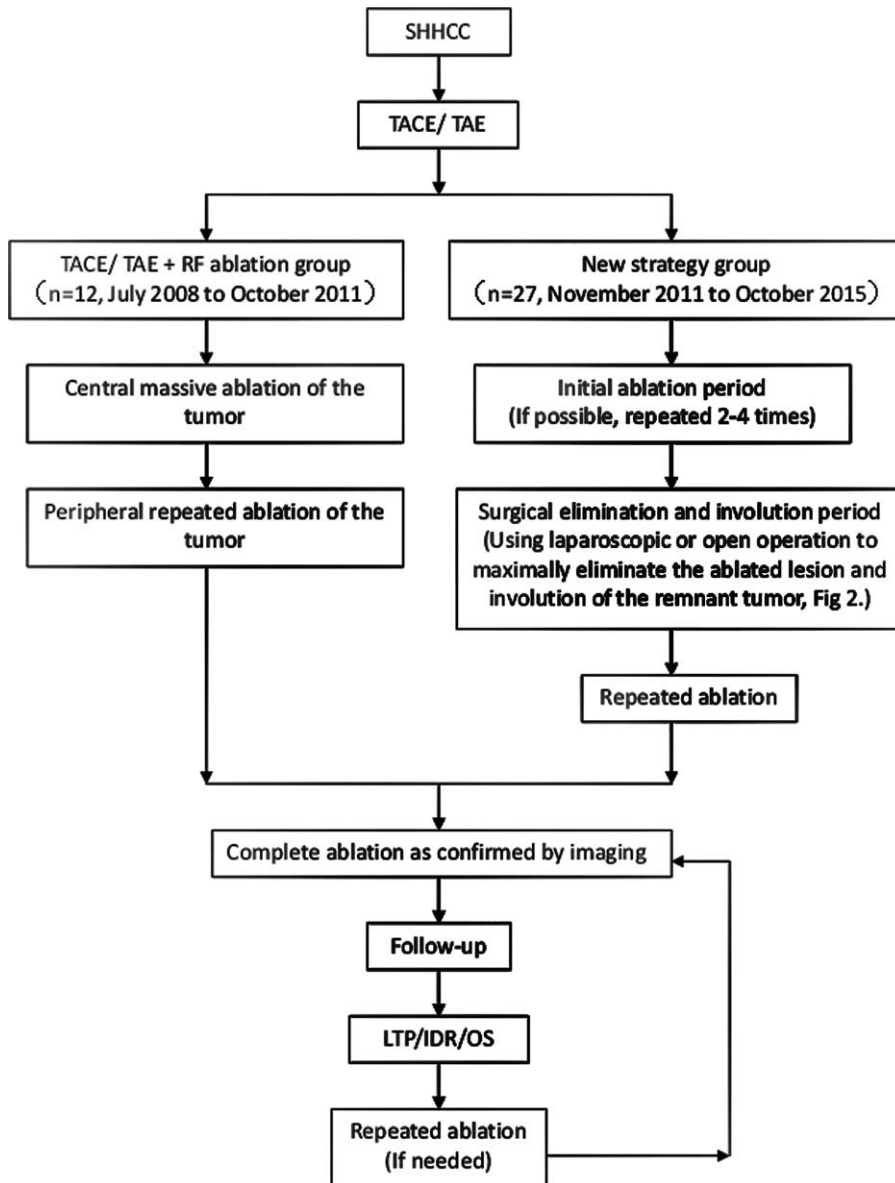


FIGURE 1. Flow diagram of the enrollment and follow-up. A total of 39 patients met the inclusion criteria. HCC = hepatocellular carcinoma, IDR = intrahepatic distant recurrence, LTP = local tumor progression, OS = overall survival, RF = radiofrequency, TACE = transcatheter arterial chemoembolization, TAE = transarterial embolization.

soon as the patient had recovered from the initial ablation period. In this procedure, a laparoscopic or open surgery was selected based on the patient’s clinical conditions at the time and medical history. When performing a laparoscopic operation, we used 3 to 4 laparoscopic ports (5–10 mm in diameter), placed according to the tumor location. A 10-mm subumbilical port was used for the laparoscope. A second trocar was inserted in the right or left upper quadrant (for right or left liver lesions, respectively, and according to liver anatomy), for the passage of the ultrasound probe. We performed an open operation via right subcostal incisions with or without upward midline extensions. In all cases, intraoperative ultrasound was used to facilitate the marking of an elimination line for the ablated lesion and to rule out previously undetected lesions. Coagulative desiccation was

performed 1 cm outside the line using Cool-tip ACTC2025 or ACTC1525 electrodes and an RF generator (Covidien Healthcare). The procedure for the elimination and involution is shown in Figures 2 and 3. Briefly, the ablated tumor was removed in a block-by-block, superficial-to-deep manner, and was further ablated and subsequently removed as much as possible to maximize its elimination. Hepatic margins were involuted to confine the remaining lesion into an ellipsoid, as we previously described.²⁰ The remaining tumor in the ellipsoid area was subsequently treated with percutaneous RF ablation. In some situations, when the hepatic margins did not need to be involuted, a drainage tube was left in the remnant cavity. Implementing intra-abdominal drainage was left to the operating surgeon’s discretion. Phase 3: Repeated percutaneous RF

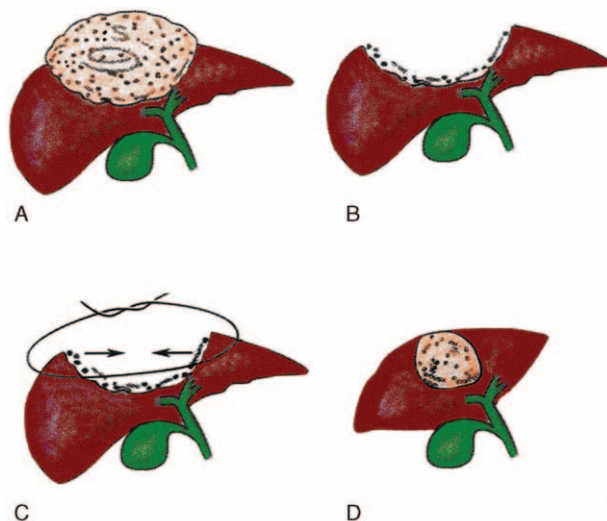


FIGURE 2. Procedure of surgical elimination of the ablated lesion and involution of the remnant tumor. (A) Prior to surgical elimination and involution. (B) After surgical elimination of the ablated lesion. (C) Involution of the remnant tumor. (D) After involution.

ablation, if needed. One month postoperatively, AFP level was examined and the lesion was analyzed by an enhanced CT or MRI scan to determine whether a sufficient AM had been achieved and whether remnant or recurrent tumors were present. Any remnant or recurrent tumors were treated with repeated percutaneous RF ablation. If the AM of the tumor was <1.0 cm in the new strategy group, repeated percutaneous RF ablation was recommended. This new strategy for treating SHHCC is shown schematically in Figures 1 and 2.

Image Analysis and Post-Treatment Assessment

Tumor response to RF ablation was assessed by CT or MRI scan 1 month after ablation. The interpretation of the imaging findings was made based on the consensus of 2 abdominal radiologists with 12 and 15 years of experience in abdominal imaging. The imaging evaluators were aware of the medical history of the patients. The morphologies and enhancement patterns of the treated lesions were recorded and compared with those before treatment. AM was evaluated as described previously.²¹ AM was defined as a narrow hypointense band around the contrast-enhanced area. When it is difficult to measure the AM due to the heterogeneous enhancement in the tumors, we carefully compared the imaging findings before and after the final RF ablation, outlined the contours of the treated tumors, and then defined and measured the AM based on the tumor contour rather than the margin of the contrast enhancement.

When no enhancement was seen in the treated lesion, we consider a complete ablation was achieved. An existence of nodular or irregular enhancement on the arterial phase contrast-enhanced CT or MR images indicated an incomplete tumor ablation. LTP was defined as the nodular lesion located in the peripheral margin of the low-attenuated ablated zone and enhanced on the hepatic arterial phase contrast-enhanced images and washed out on the delayed phase. Intrahepatic distant recurrence (IDR) was defined as the lesion with similar imaging characteristics but absence of a direct contact with the original ablated zone. Overall survival (OS) was evaluated as well, which was defined as the interval between the date of

primary therapy and the date of death or the last follow-up examination of patients still alive.²¹ Upon the confirmation of LTP or IDR, patients were referred for additional session(s) of percutaneous RF ablation. The numbers of ablation sessions, the amount of thermal energy delivered per treatment and the duration of ablation were recorded. RF ablations were repeated until no LTP or IDR was detected. Clinical follow-up, including an AFP assay, was performed monthly for the 1st year and subsequently every 2 or 3 months.

Postablation morbidities were categorized into minor and major complications. Minor complications were those who could be treated conservatively or resolved by oral or intravenous medication without further interventions. Major complications are those who need an intensive care unit stay, treatment by an interventional or a surgical procedure.

Statistical Analysis

Continuous data are expressed as mean \pm standard deviation. Comparisons were made using the Mann–Whitney *U* test. Categorical data were compared using the Fisher exact test. The cumulative LTP-free or IDR-free survival time and OS time were estimated using the Kaplan–Meier method and compared using the log-rank test. Cox regression tests were used for univariate comparisons. If multiple risk factors were shown to be significant by this test, we performed multivariate analysis using Cox proportional hazards regression model to identify the independent prognostic factors for LTP, IDR, and OS. Correlation analysis between prognostic factors and LTP, IDR, and OS was performed using Spearman and Pearson coefficients analysis. All statistical analyses were conducted using SPSS 15.0 statistical software (SPSS Inc., Chicago, IL). $P < 0.05$ was considered to indicate a significant difference.

RESULTS

Clinicopathological Characteristics

The clinical and follow-up data of the 39 patients with SHHCC are summarized in Table 1. Among these patients, 12 were treated only with TACE/TAE and repeated RF ablation and the remaining 27 were treated with the new strategy. All of the tumors were located mainly in the right liver lobe, with 13 tumors also involving the left liver lobe. The clinicopathological characteristics of the 2 groups are shown in Table 1. No significant differences were observed in sex, age, pre-existing hepatitis, Child–Pugh grading, model for end-stage liver disease (MELD) score, preoperative AFP level, etiology of liver cirrhosis, biochemical analysis results such as aspartate aminotransferase and alanine aminotransferase, tumor size, cell differentiation, and follow-up period.

Postoperative Data and Safety

As summarized in Table 2, the number of RF ablation sessions before complete ablation as confirmed by imaging was much greater in the TACE/TAE + RF ablation group than in the new strategy group ($P = 0.002$). The AM at the time of imaging complete ablation was significantly smaller in the TACE/TAE + RF ablation group than in the new strategy group ($P < 0.001$).

No procedure-related mortality occurred. The minor complications were fever from 38 to 39°C, general malaise or pain, and asymptomatic right pleural effusion. The major complications were pneumothorax, hemopneumothorax, liver abscess, and intra-abdominal hemorrhage. One patient in the TACE/

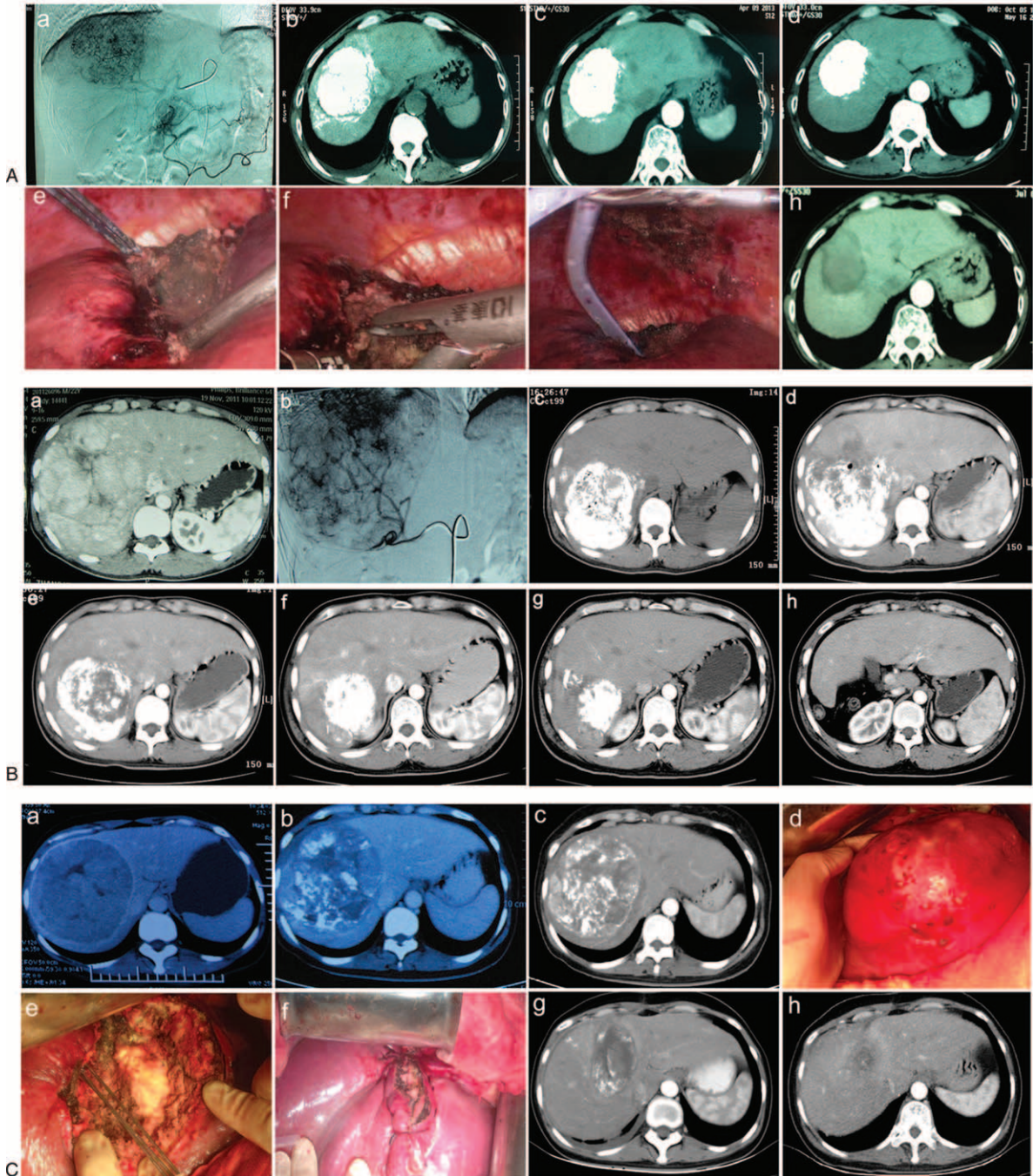


FIGURE 3. Three typical cases of SHHCC treated by the new strategy. (A) The first case of SHHCC: (a) TACE; (b) CT scan after TACE; (c) CT scan after the first RF ablation in the initial ablation period; (d) CT scan after the second RF ablation in the initial ablation period; (e–g) laparoscopic elimination of the ablated lesion and a drainage tube left in the residual cavity; (h) CT scan 1 month after the laparoscopic operation. (B) The second case of SHHCC: (a) CT scan before TACE; (b) TACE; (c) CT scan after TACE; (d–g) CT scan after the 1st to 4th RF ablations in the initial ablation period (compensatory hyperplasia of the left lobe could be detected); (h) CT scans at the time of complete ablation as confirmed by imaging. (C) The 3rd case of SHHCC: (a) CT scan before TACE; (b) CT scan after TACE; (c) CT scan after 2 RF ablation sessions in the initial ablation period; (d–f) the procedure of surgical elimination of the ablated lesion and involution of the remnant tumor; (g) CT scan half a month after surgery; (h) the CT scan at the time of imaging complete ablation. CT = computed tomography, RF = radiofrequency, SHHCC = solitary huge hepatocellular carcinoma, TACE = transarterial chemoembolization.

TABLE 1. Clinicopathological Characteristics Between the TACE/TAE + RF Ablation Group and the New Strategy Group

Variables	Treatment		P Value
	TACE/TAE + RF Ablation (n = 12)	New Strategy (n = 27)	
Age, y	57 (48–69)	54 (21–71)	0.987
Gender			
Male/female	10 (83.3)/2 (16.7)	21 (77.8)/6 (22.2)	0.692
Pre-existing hepatitis			
Hepatitis B	12 (100)	23 (85.2)	0.576
Hepatitis C	0 (0.0)	1 (3.7)	0.518
Child–Pugh grading			
Class A/class B	7 (58.3)/5 (41.7)	16 (59.3)/11 (40.7)	0.957
Liver cirrhosis			
Yes/no	9 (75.0)/3 (25.0)	19 (70.4)/8 (29.6)	0.767
Serum AFP level, ng/mL			
<20	1 (8.3)	2 (7.4)	0.920
20–200	4 (33.3)	10 (37.0)	0.824
>200	7 (58.4)	15 (55.6)	0.872
Biochemical analysis			
AST, IU/L	80.2 (16.5–261.4)	66.8 (21.4–235.8)	0.575
ALT, IU/L	61.9 (11.4–242.5)	62.2 (16.5–253.0)	0.312
Alb, g/dL	3.3 (2.8–4.1)	3.2 (2.7–3.9)	0.643
T-Bil, mg/dL	0.8 (0.3–2.8)	0.9 (0.4–3.0)	0.378
ALP, IU/L	102.2 (7.9–386.5)	84.8 (8.7–391.1)	0.554
PT, %	79 (59–100)	83.4 (61–100)	0.192
AFP, ng/mL	213.2 (9.3–11,302.5)	207.6 (11.3–8351.7)	0.911
Tumor diameter, cm	11.5 (10.2–13.5)	11.9 (10.2–15.8)	0.109
MELD score	8.5 (6–14)	9.0 (6–16)	0.908
TACE/TAE	5 (41.7)/7 (58.3)	10 (37)/17 (63)	0.784
Cell differentiation			
Well	8	16	0.661
Well to moderate	4	10	0.824
Poor	0	1	0.499
Follow-up period, mo	25.4 (9–71)	25.8 (9–47)	0.267

Values presented as absolute numbers (percent of cases) or median (range). Fisher exact test or Mann–Whitney *U* test.

AFP = alpha-fetoprotein, Alb = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AST = aspartate aminotransferase, MELD = model for end-stage liver disease, PT = prothrombin time, RF = radiofrequency, TACE = transarterial chemoembolization, TAE = transarterial embolization, T-Bil = total bilirubin.

TAE + RF ablation group experienced massive peritoneal hemorrhage immediately after her second RF ablation treatment. She recovered the following day with conservative therapy, including blood transfusion. One patient in the TACE/TAE + RF ablation group experienced liver abscess and was finally cured by percutaneous aspiration under CT guidance. Two patients in the new strategy group developed pneumothorax, who was successfully treated by chest tube placement. One patient in the new strategy group developed hemopneumothorax and recovered from chest tightness and chest tube placement. There were no significant differences between the 2 groups not only for minor complications ($P=0.401$) but also for major ones ($P=0.632$).

LTP-Free Survival, IDR-Free Survival, and OS

During the follow-up, LTP was found in 10 (83.3%) of 12 patients in the TACE/TAE + RF ablation group and in 11 (40.7%) of 27 patients in the new strategy group ($P=0.014$; Table 2). The 1-, 2-, and 3-year LTP-free survival rates were 58.3%, 29.2%, and 9.7% in the TACE/TAE + RF ablation

group and 82.9%, 73.9%, and 18.5% in the new strategy group (Figure 4A), respectively, and differed significantly between these 2 groups ($P=0.002$).

IDR was found in 11 (91.7%) of 12 patients in the TACE/TAE + RF ablation group and 11 (40.7%) of 27 patients in the new strategy group (Table 2). There was a significant difference in the rates of total IDR between the TACE/TAE + RF ablation group and the new strategy group (91.7% vs 40.7%, $P=0.003$). The 1-, 2-, and 3-year IDR-free survival rates were 66.7%, 28.6%, and 9.5% in the TACE/TAE + RF ablation group and 92.0%, 78.1%, and 17.2% in the new strategy group, respectively (Figure 4B); there was no significant difference between these 2 groups ($P=0.108$).

As of October 2015 (with a median follow-up of 25.7 months), 16 patients (41.0%) remained alive and 23 (59.0%) had died, namely, 12 patients in the TACE/TAE + RF ablation group and 11 patients in the new strategy group. The cause of death was HCC in 19 patients (82.6%) and liver failure in 4 (17.4%). The 1-, 2-, and 3-year OS rates were 75.0%, 33.3%, and 16.7% in the TACE/TAE + RF ablation group and 92.0%, 84.0%, and 32.7% in the new strategy group (Figure 4C),

TABLE 2. Postoperative Data Between the TACE/TAE + RF Ablation Group and the New Strategy Group

Variables	Treatment		P Value
	TACE/TAE + RF Ablation (n = 12)	New Strategy (n = 27)	
No. of RF ablation sessions before imaging complete ablation	8.1 (6–11)	6.5 (5–8)	0.002
AM at the time of imaging complete ablation, cm	0.4 (0.3–1.2)	1.5 (1.0–2.1)	<0.001
Complication			
Minor	8 (66.7)	19 (70.4)	0.401
Major	2 (16.7)	3 (11.1)	0.632
Recurrence pattern			
LTP only	1 (8.3)	5 (18.5)	0.416
IDR only	2 (16.7)	5 (18.5)	0.889
LTP + IDR	9 (75.0)	6 (22.2)	0.002
Total LTP	10 (83.3)	11 (40.7)	0.014
Total IDR	11 (91.7)	11 (40.7)	0.003

Values presented as absolute numbers (percent of cases) or median (range). Fisher exact test or Mann–Whitney *U* test.

AM = ablative margin, IDR = intrahepatic distant recurrence, LTP = local tumor progression, RF = radiofrequency, TACE = transarterial chemoembolization, TAE = transarterial embolization.

respectively; the 2 groups differed significantly ($P = 0.025$, log-rank test).

Factors Associated With LTP, IDR, and OS

Using univariate analysis, AFP (>200 ng/mL), AM (>1.0 cm), and well-differentiated cells were found to be significant factors for predicting LTP, IDR, and OS (Table 3). Surgical elimination was found to be a significant factor only for predicting OS (Table 3). The results of multivariate analyses of the 4 above-mentioned factors that were found to be significant in the univariate analysis are shown in Table 4, as the hazard ratios (HRs). AFP (>200 ng/mL), AM (>1.0 cm), and well-differentiated cells were found to be significant independent factors linked to LTP, IDR, and OS. Next, to explore the correlation between the AM and the other prognostic factors, we performed a correlation analysis. It was found that the AM was strongly associated with surgical elimination ($P < 0.001$, correlation coefficient = 0.877), which suggested the key role of surgical elimination in achieving a sufficient AM for patients with SHHCC who have been treated mainly with RF ablation.

DISCUSSION

Despite improvements in HCC treatment, large HCC, especially ≥ 10 cm, remains a major challenge. In the past few years, we have observed a special subtype of HCC ≥ 10 cm, defined as SHHCC and exhibiting less metastatic capacity.⁹ Yang et al²² reported that the clinical and pathological characteristics and outcome after hepatic resection of some SHHCC cases are similar to those of small HCC, but significantly better than those of nodular HCC. However, the vast majority of such patients are not eligible for resection because of the severity of underlying cirrhosis when SHHCC is detected. We previously demonstrated that SHHCC could be completely ablated, as indicated by temporary imaging findings, using a well-designed strategy featuring repeated RF ablation.⁹ Unfortunately, the recurrence rate of SHHCC remained very high because of an insufficient AM, thus reducing the long-term survival of these patients.

It was previously found that the majority of recurrent lesions emerge from the ablated area within 0.5 cm of the tumor border, which is the area most likely to contain viable tumor cells.²³ Thus, an AM of 0.5 to 1.0 cm was broadly accepted at most institutions. However, we found that, for HCC tumors of 3.1 to 5.0 cm, an AM > 1.0 cm could significantly reduce the rate of recurrence compared with an AM of 0.5 to 1.0 cm, which emphasizes the need for more defensive strategies in using an AM wider than 1.0 cm for the ablation of HCC tumors of 3.1 to 5.0 cm.²¹ However, for SHHCC, it is very difficult to achieve an AM of 0.5 to 1.0 cm using a traditional RF strategy, let alone achieving an AM > 1.0 cm. In October 2004, we successfully treated a patient with spontaneously ruptured huge 14-cm HCC located in medial lobe.²⁰ A primary emergent RF ablation applied at multiple spots was performed to achieve hemostasis, coagulation, and cytorreduction of the lesion followed by ablation to eradicate the viable tumor as much as possible. The adjacent hepatic capsule and parenchyma were involuted to confine the remaining lesion in an ellipsoid entity. The residual viable tumor in the ellipsoid area was subsequently treated by multiple sessions of RF ablation. The patient has survived for 11 years. This successful case prompted us to develop the new combined strategy in this study, which may be helpful to achieve a sufficient AM for SHHCC, thus improving patient survival.

In this study, a new strategy including TACE/TAE + repeated RF ablation and eliminating ablated lesion-oriented laparoscopic or open surgery was introduced for the treatment of patients with SHHCC. It was found that we could perform fewer RF ablation sessions to achieve complete ablation as confirmed by imaging using this new strategy. In addition, the AM at the time of imaging complete ablation was significantly smaller in the TACE/TAE + RF ablation group than in the new strategy group (median 1.5 cm). The 1-, 2-, and 3-year LTP-free survival rates and the OS rates were significantly higher in the new strategy group than in the TACE/TAE + RF ablation group. However, this new strategy had no effect on the IDR-free survival rate. Interestingly, the longest surviving patient of the TACE/TAE + RF ablation group had an AM of 1.2 cm. This

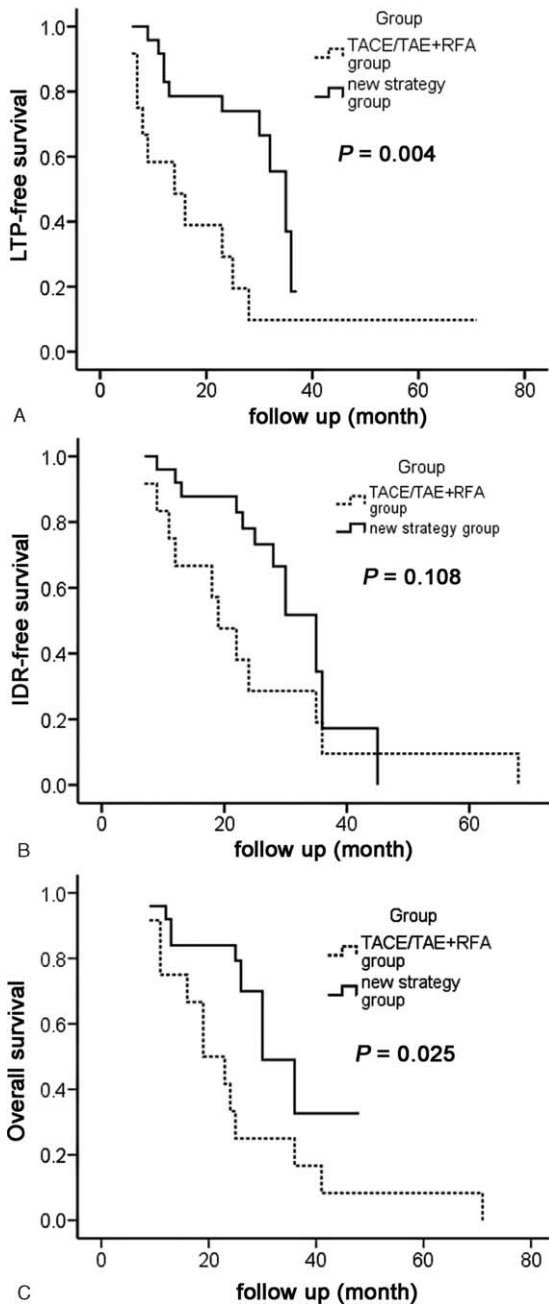


FIGURE 4. Kaplan–Meier analysis of the TACE/TAE + RF ablation group and the new strategy group. (A) The local tumor progression (LTP)-free survival rates. The 1-, 2-, and 3-y LTP-free survival rates were 58.3%, 29.2%, and 9.7% in the TACE/TAE + RF ablation group and 82.9%, 73.9%, and 18.5% in the new strategy group, respectively ($P=0.023$). (B) The intrahepatic distant recurrence (IDR)-free survival rates. The 1-, 2-, and 3-y IDR-free survival rates were 66.7%, 28.6%, and 9.5% in the TACE/TAE + RF ablation group and 92.0%, 78.1%, and 17.2% in the new strategy group, respectively ($P=0.108$). (C) The overall survival (OS) rates. The 1-, 2-, and 3-y OS rates were 75.0%, 33.3%, and 16.7% in the TACE/TAE + RF ablation group and 92.0%, 84.0%, and 32.7% in the new strategy group, respectively ($P=0.025$). RF = radiofrequency, TACE = transarterial chemoembolization, TAE = transarterial embolization.

TABLE 3. Significant Variables in the Univariate Analysis for LTP, IDR, and OS (n = 39)

Significant Variables	n	P Value		
		LTP	IDR	OS
Age (>65 y), yes/no	9/30	0.092	0.538	0.462
Gender (male), yes/no	31/8	0.669	0.052	0.467
Liver cirrhosis, yes/no	28/11	0.084	0.733	0.574
Child–Pugh grading (class B), yes/no	16/23	0.138	0.156	0.914
AST (>40 IU/L), yes/no	27/12	0.683	0.088	0.801
ALT (>40 IU/L), yes/no	29/10	0.392	0.192	0.969
ALP (>110 IU/L), yes/no	13/26	0.667	0.055	0.247
Alb (>3.5 g/dL), yes/no	10/29	0.624	0.367	0.108
T-Bil (>1 mg/dL), yes/no	10/29	0.364	0.364	0.746
PT (>70%), yes/no	30/9	0.275	0.876	0.925
AFP (>200 ng/mL), yes/no	22/17	0.001	<0.001	0.001
Surgical elimination, yes/no	27/12	0.598	0.462	0.036
AM (>1.0 cm), yes/no	28/11	0.009	0.002	0.001
Cell differentiation (well), yes/no	24/15	0.031	0.014	0.020
Post-RF ablation antiviral therapy, yes/no	28/11	0.918	0.353	0.428

AFP = alpha-fetoprotein, Alb = albumin, ALP = alkaline phosphatase, ALT = alanine aminotransferase, AM = ablative margin, AST = aspartate aminotransferase, IDR = intrahepatic distant recurrence, LTP = local tumor progression, OS = overall survival, PT = prothrombin time, RF = radiofrequency, T-Bil = total bilirubin.

patient experienced a liver abscess during the repeated RF ablation procedures. This abscess was finally cured by percutaneous aspiration under CT guidance. Although this abscess prolonged the patient’s hospital stay, it did dramatically reduce the tumor size of SHHCC, allowing a sufficiently small AM to be achieved. This patient eventually survived for 71 months.

Our study has limitations. First, we treated patients using different RF devices because remarkable advancement of RF ablation technologies occurred over a period of time of 7 years. Second, this is a single-centered retrospective study with a small sample of subjects involved due to the relatively low incidence of SHHCC. Third, the total procedure times over a long course of treatments are much longer than open surgery alone. However, the short recovery time and improved quality of life after the combination therapies might be superior to surgery alone, which result from the benefit of laparoscopy-aided tumor eliminations and involutions (23/27, 85.2%). The advantages of the combination therapies reported in this study need to be further verified in multiple centers with an involvement of large cohort of patients. Nevertheless our study may provide some helpful clues for hepatobiliary physicians in selecting the optimal treatments for patients with SHHCC and may provide a basis for the design of clinical trials.

The findings from our study indicate that repeated RF ablation plus surgical elimination of the ablated lesion and involution of the remnant tumor following TACE/TAE should now be considered as an alternative treatment for patients with SHHCC who were initially excluded from surgery.

TABLE 4. Significant Variables in the Multivariate Analysis for LTP, IDR, and OS (n = 39)

Significant Variables	LTP			IDR			OS		
	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value	Hazard Ratio	95% CI	P Value
AFP (>200 ng/mL), yes/no	0.153	0.042–0.558	0.004	0.046	0.010–0.219	<0.001	0.048	0.010–0.227	<0.001
AM (>1.0 cm), yes/no	15.228	4.132–56.126	<0.001	24.955	6.017–103.488	<0.001	12.097	3.731–39.220	<0.001
Cell differentiation (well), yes/no	3.811	1.591–9.125	0.003	4.715	1.661–13.387	0.004	4.521	1.671–12.229	0.003

AFP = alpha-fetoprotein, AM = ablative margin, CI = confidence interval, IDR = intrahepatic distant recurrence, LTP = local tumor progression, OS = overall survival.

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